REMARKS

Claim Amendments

Claims 1, 7, and 15-35 are pending. Claims 1 and 7 are amended. Claims 15-32 stand withdrawn. Claim 39 is canceled without prejudice or disclaimer to the subject matter therein. Support for the claim amendments may be found throughout the specification and in the claims as originally filed. *See e.g.*, ¶¶ [0011], [0012].

Applicants respectfully submit that the claim amendments reduce issues for appeal, are per the Examiner's suggestion, and do not introduce new matter. Accordingly, Applicants respectfully request entry of the above amendments.

Statement of Substance of Interview Under 37 C.F.R. § 1.133(b)

In accordance with 37 C.F.R. § 1.133(b) and M.P.E.P. § 713.04, Applicants provide a summary of the interview of August 12, 2008. Applicants thank Examiners Deborah Crouch and Marcia Noble for agreeing to conduct the interview and appreciate the courtesies extended by the Examiners.

During the interview, the parties discussed the association between decreased AOP-1 expression and chronic heart disease, ischemic heart failure, and ischemic heart disease as well as therapeutic models for these conditions taught by the specification. The Examiners suggested that claim 1 be amended to recite "heart disease associated with decreased levels of AOP-1."

Applicants have amended claim 1 in accordance with the Examiners' suggestion.

Rejection under 35 U.S.C. § 112, First Paragraph — Enablement

Claims 1, 7, 33-35, and 39 stand rejected under 35 U.S.C. § 112, first paragraph as allegedly failing to comply with the enablement requirement.

Applicants respectfully disagree and traverse this rejection for at least the following reasons: (1) Applicants have provided evidence that one of skill in the art would reasonably conclude that the specification teaches a therapeutic association between AOP-1 and treatment of heart disease (i.e., the administration of the AOP-1 gene would be useful in treating heart disease); (2) the Office Action fails to provide evidence showing that one of ordinary skill in the art would reasonably doubt Applicants' asserted utility; (3) the Federal Circuit has held that enablement rejections similar to the instant rejection are improper; and (4) Applicants have amended claim 1 to recite "heart" disease as suggested by the Examiners.

A. The Full Scope Of The Claimed Invention Is Enabled

The claimed invention is directed to therapeutic methods comprising administering an AOP-1 gene to heart cells to treat heart disease.

Applicants have demonstrated an association between decreased AOP-1 expression and chronic heart disease, ischemic heart failure, and ischemic heart disease.[1] Applicants have also shown that the administration of AOP-1 gene results in improved cardiac function *in vitro* and *in vivo*.[2]

For example, the specification teaches that forced expression of AOP-1 protects rat cardiac cells that are exposed to hypoxic conditions and then undergo reperfusion—types of cellular injuries that are common to a variety of heart diseases.[3] Cells that had been transfected with the AOP-1 gene showed increased viability and autonomous pulsation after hypoxic and reperfusion injury, as compared to control cells not transfected with AOP-1.[4] When rat hearts are subjected to ischemic injury and reperfusion injury via the Langendorff method, those hearts that have been transfected with AOP-1 show significantly better recovery of function and decreased cell necrosis as compared to control hearts.[5]

In view of the foregoing evidence, Applicants respectfully submit that one of skill in the art would reasonably conclude that the specification teaches a therapeutic association between AOP-1 and treatment of heart disease (i.e., the administration of the AOP-1 gene would be useful in treating heart disease).[6]

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[1] *See, e.g.*, Specification at ¶ [0070]; Example 2 ("The results showed decreased expression of AOP-1 gene with the progress of the pathology of chronic heart failure in all the models."); *see also* Office Action, page 4.

[2] *See, e.g.*, Specification at ¶¶ [0071]-[0074]; Examples 7, 15, and 16.

[3] *See id.* at Example 7.

[4] *Id.*; *see also* Matsushima et al., "Overexpression of Mitochondrial Peroxiredoxin-3 Prevents Left Ventricular Remodeling and Failure after Myocardial Infarction in Mice," *Circulation* 113: 1779-86 (2006).

[5] Specification at Example 16.

[6] Indeed, the evidence of record (e.g., *in vitro* and *in vivo* assays taught in the specification, peer-reviewed publications, etc.) demonstrates that Applicants have established a reasonable correlation of the AOP-1 activity and heart disease. *See* M.P.E.P. § 2107.03, I. ("The applicant does not have to prove that a correlation exists between a particular activity and an asserted therapeutic (continued...)

B. The Office Action Fails To Establish A *Prima Facie* Enablement Rejection

To comply with the enablement requirement, the claimed invention must be enabled so that any person skilled in the art can ***make and use*** the invention without undue experimentation.[7]

The Office Action does not contend that one of skill in the art would be unable to make and use the claimed invention without undue experimentation. Rather, the Office Action asserts that the specification and evidence of record "do not demonstrate that treatment with AOP-1 gene therapy will have a therapeutic effect on ischemic heart disease, chronic heart failure, and ischemic heart failure as claimed."[8] Accordingly, the Office Action appears to question whether the claimed method would be *useful* (i.e., have utility) for treating heart disease.[9]

To challenge an asserted utility, the USPTO must provide evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility.[10] Applicants respectfully submit that the USPTO has not met its burden.

The only evidence cited to support the Office Action's assertion of a lack of therapeutic effectiveness is Skrzvpeic-Spring et al., "Isolated Heart Perfusion According to Langendorff—Still Viable in the New Millennium," 55: 113-126, 2007. This reference does not question the usefulness of administering a nucleic acid that enhances the production of AOP-1, or provide any evidence to cause one of skill in the art to question the asserted utility of such an administration. Rather, the reference provides a review of the Langendorff method—a method used in the instant specification.

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use of a compound as a matter of statistical certainty, nor does he or she have to provide actual evidence of success in treating humans where such a utility is asserted. Instead, as the courts have repeatedly held, all that is required is a reasonable correlation between the activity and the asserted use."); *id.* at II. ("If reasonably correlated to the particular therapeutic or pharmacological utility, data generated using *in vitro* assays, or from testing in an animal model or a combination thereof almost invariably will be sufficient to establish therapeutic or pharmacological utility for a compound, composition or process.").

[7] *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (emphasis added).

[8] Office Action, p. 4.

[9] This, however, appears to be a Section 101 issue, rather than Section 112. *See In re Brana*, 34 U.S.P.Q.2d 1436, 1440-1441 (Fed. Cir. 1995).

[10] *See id.* at 1441; *see also* M.P.E.P. § 2164.07, I.B.

As the title of the reference suggests, the authors conclude that the Langendorff method is viable model for the study of heart disease:

> The isolated perfused heart according to Langendorff has served as a robust model for many fundamental discoveries in cardiac physiology, pathology and pharmacology for more than 100 years. Only few experimental models have enjoyed such an undiminished popularity over such a long time. It is still one of the most popular experimental designs in cardiovascular research and cardiovascular pharmacology. The disadvantages the model may suffer are outweighed by its benefits and the technique possesses an optimal balance of both quality and quantity of date with clear clinical relevance.[11]

Nonetheless, the Office Action contends that Langendorff method is "not an appropriate model for ischemic heart disease."[12] The Office Action also asserts that "the results extrapolated from this method can not predictably be extrapolated to a therapeutic method of ischemic heart disease that administers an AOP-1 gene as claimed."

Applicants respectfully disagree. Applicants submit that the Office Action quotes Skrzypiec-Spring et al. out of context to assert that the Langendorff method is not an appropriate model. Specifically, the Office Action refers to the statement that "there are some limitations of the [Langendorff] method including the absence of normal humoral influences and neuronal regulation..."[13] The Office Action's reference to this statement ignores the rest of the same sentence, which states "the impact of these shortcomings is limited by the very advantage that much important first hand information can be gained by virtue of the elegant simplicity of this technique."[14] Indeed, as discussed above, Skrzypiec-Spring et al. concludes that the benefits of the Langendorff method outweigh any of its disadvantages.

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[11] Skrzvpeic-Spring et al., page 124.

[12] Office Action, page 5. Applicants note that the USPTO previously acknowledged that the Langendorff model "is an art accepted model for studying the biochemical and histological effects of ischemia on the heart" and that the specification "provides an experimental model that assesses ischemia in the rat heart following treatment with an AOP-1 expression vector." Office Action of January 28, 2008, p. 7.

[13] Skrzypiec-Spring et al., p. 113; *see also* Office Action, p. 5.

[14] Skrzypiec-Spring et al., p. 113.

The Office Action invites Applicants to provide evidence that the Langendorff method is an acceptable therapeutic model.[15] Applicants respectfully submit that Skrzypiec-Spring et al. provides such evidence. For example, Skrzypiec-Spring et al. states:

> [the Langendorff method is] a very useful tool in modern cardiovascular and pharmacological research ... ***the method has brought many important advances in many areas including ischemia-reperfusion injury***, cell-based therapy ...[16]

> Today a variety of ***cardiovascular researchers still use this vital technique*** in [a] myriad [of] ways ***to investigate*** the heart, from the study of the effect of a single gene alteration on heart physiology, to ***novel therapeutic means to protect the heart from ischemia and other insults.***[17]

> [the Langendorff method is] a ***very important tool in studies of pathological conditions which would normally pose a threat to the survival of the animal in an in vivo*** experiment[18]

> The isolated heart model is ***well suited to study the effects of ischemia and hypoxia.***[19]

> The Langendorff heart is ***ideal for the screening of cardiac and non-cardiac drugs*** for their effects on heart condition.[20]

> Hardly any other procedure has resulted in such ***a great contribution to cardiovascular physiology and pharmacology and*** is still actively being used today as ***a valuable tool in cardiovascular research.***[21]

In view of the foregoing, Applicants submit that Skrzypiec-Spring et al. teaches that the Langendorff model is an appropriate therapeutic model for heart diseases such as ischemic heart disease.[22]

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[15] *See* Office Action, p. 5.

[16] Skrzypiec-Spring et al. at abstract.

[17] *Id.* at p. 113.

[18] *Id.* at p. 117.

[19] *Id.* at p. 120.

[20] *Id.* at p. 122.

[21] *Id.* at p. 123.

C. The Instant Case Is Analogous To *In re Brana*

Applicants submit that the enablement rejection imposes an impermissibly high standard for utility of a therapeutic invention. Indeed, the Federal Circuit has made clear that enablement rejections based on allegations of lack of utility are inappropriate merely because the therapeutic effectiveness of the treatment has not yet been proven in humans.[23]

In *In re Brana*, the Federal Circuit overturned a Board of Patent Appeals and Interferences' decision affirming an enablement rejection of a claim directed to antitumor compounds for allegedly failing to establish that the compounds had antitumor activity in humans.[24] The Applicants in *Brana* based their assertions of antitumor activity on tests conducted in mouse models.[25] In response, the Board cited references that questioned the therapeutic predictive value of *in vivo* murine tests.

The Federal Circuit held that the USPTO did not met its initial burden of challenging Applicants' asserted utility. The court explained:

> The references cited by the Board, Pazdur and Martin, do not question the usefulness of any compound as an antitumor agent or provide any other evidence to cause one of skill in the art to question the asserted utility of applicants' compounds. Rather, these references merely discuss the therapeutic predictive value of *in vivo* murine tests -- relevant only if applicants must prove the ultimate value in humans of their asserted utility.[26]

The court concluded that such proof is not required for patentability:

> Usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans.[27]

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[22] To the extent that the Office Action is requiring that Applicants provide human *in vivo* data, Applicants respectfully submit that such a requirement is improper under case law and USPTO procedure. *See In re Brana*, 34 U.S.P.Q.2d at 1442; M.P.E.P. § 2107.03, IV.

[23] *In re Brana*, 34 U.S.P.Q.2d at 1442.

[24] *Id.* at 1437-39.

[25] *Id.* at 1440.

[26] *Id.* at 1441.

[27] *Id.* at 1442

Rather, the Federal Circuit cited precedent that "proof of an alleged pharmaceutical property for a compound by statistically significant tests with standard experimental animals is sufficient to establish utility."[28]

The instant case presents a factual scenario similar to *Brana*. Like the Applicants in *Brana*, the instant specification teaches an *in vivo* rat model that correlates activity (i.e., AOP-1 activity) and an asserted utility (e.g., improved cardiac function).[29] The instant specification also teaches that transfection of rat cardiac cells with AOP-1 causes those cardiac cells to exhibit significantly improved survivability and autonomous pulsation, as compared to non-treated cardiac cells under hypoxic conditions (e.g., which can be caused by loss of blood flow during ischemic chronic heart failure and chronic heart failure).[30] Applicants have also provided other evidence of utility (e.g., peer-reviewed publications).[31]

The only evidence cited to rebut Applicants showing is Skrzvpeic-Spring et al. As discussed above, Skrzvpeic-Spring et al. does not question the utility of the claimed invention. Rather, Skrzvpeic-Spring et al. actually supports Applicants assertion that its *in vivo* model is appropriate.

Accordingly, because Applicants have satisfied the standard for enablement set forth in *Brana* and the USPTO has failed to met its initial burden of challenging Applicants' asserted utility, Applicants respectfully request withdrawal of the enablement rejection.

D. Matsushima Supports Applicants Asserted Utility

The Office Action contends that Matsushima does not support the enablement of the claimed invention.[32] The Office Action acknowledges that Matsushima teaches "[o]verexpression of AOP-1 in transgenic mice protected against induced myocardial infarction in said mice."[33]

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[28] *Id.* (citing *In re Krimmel*, 292 F.2d 948, 953, 130 U.S.P.Q. 215, 219 (C.C.P.A. 1961)).

[29] *See, e.g.*, Specification at Example 16.

[30] *Id.* at Example 7.

[31] *See, e.g.*, Brixius et al., "Isoform-Specific Downregulation of Peroxiredoxin in Human Failing Myocardium," *Life Science* 81(10): 823-831 (2007); Matsushima et al., "Overexpression of Mitochondrial Peroxiredoxin-3 Prevents Left Ventricular Remodeling and Failure after Myocardial Infarction in Mice," *Circulation* 113: 1779-86 (2006)

[32] *See* Office Action, pp. 5-6.

[33] *Id.* at p. 6.

However, the Office Action asserts the methods of administering the AOP-1 gene in the instant case and Matsushima are different.[34]

Applicants respectfully submit that Matsushima, at a minimum, teaches that the increased expression of AOP-1 protects against certain effects of heart diseases. This is consistent with the specification's teaching that expression of AOP-1 improves cardiac function. Accordingly, Applicants submit that Matsushima supports Applicants' assertion that the administration of the AOP-1 gene would be useful in treating heart disease.

E. Applicants' Amendment Renders The Final Ground Of TheEnablement Rejection Moot

Finally, the Office Action maintains the enablement rejection on the grounds that the claims "encompass a therapeutic method for any disease associated with decreased expression of an AOP-1 gne or AOP-1 by delivering a therapeutic expression vector to the heart."[35]

As discussed above, Applicants have amended claim 1 to recite "[a] therapeutic method for a heart disease...." in accordance with the Examiners' suggestion. Accordingly, this aspect of the enablement rejection is moot.

In view of the foregoing, Applicants requestfully request withdrawal of the enablement rejection.

Rejections Under 35 U.S.C. § 112, First Paragraph — Written Description

Claims 1, 7, 33-35, and 39 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. The Office Action objects to the recitation of "a nucleic acid having sequence identity of 90% or more."

Applicants have amended claim 1 to delete the recitation of sequence identity and canceled claim 39, thereby rendering this rejection moot.

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[34] *Id.*

[35] Office Action, p. 6.

CONCLUSION

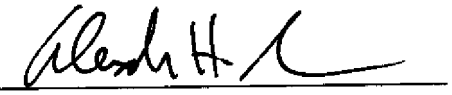
Applicants respectfully submit that claims are in condition for allowance, and such disposition is earnestly solicited. Should the Examiner believe that any issues remain after consideration of this response, the Examiner encouraged to contact the Applicants' undersigned representative to discuss and resolve such issues.

This response is being submitted within the shortened statutory period for reply. Accordingly, no fees are due. However, should the USPTO determine that any fees are due to enter and consider this response, the Commissioner is hereby authorized to charge such fees to the undersigned's **Deposit Account No. 50-0206.**

Respectfully submitted,

HUNTON & WILLIAMS LLP

Date: January 15, 2009

By: 

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